ABC of preterm birth
Evidence based care

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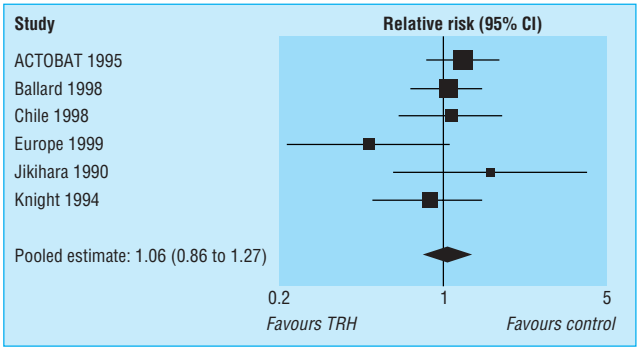
This is the last in a series of 12 articles

Evidence based practice—the integration of individual clinical expertise with the best available clinical evidence from systematic research **David Sackett**

The ethos of basing practice on the best available evidence is well established in perinatal medicine. The introduction to clinical practice of major interventions, such as antenatal corticosteroids and exogenous surfactant, was informed by evidence from seminal randomised controlled trials and systematic reviews.

Equally important has been the development and evaluation of interventions that have been shown not to have major benefits for preterm infants. For example, strong evidence from preclinical research studies indicated that antenatal thyrotropin releasing hormone might act synergistically with corticosteroids to reduce the risk of respiratory distress syndrome in preterm infants. Despite the biological plausibility of this treatment and evidence of effect in animal models, randomised controlled trials (involving over 4500 women) did not show any improvement in outcomes, including mortality, for preterm infants. Also, antenatal thyrotropin releasing hormone was shown to be associated with adverse effects for mothers and infants, including a higher risk of infants needing mechanical ventilation. On the basis of this evidence, antenatal thyrotropin releasing hormone does not have a role in the management of threatened preterm birth.



Effect of prenatal thyrotropin releasing hormone (TRH) for preterm birth on mortality before hospital discharge. Data from Crowther CA et al. *Cochrane Database Syst Rev.* 2003;(4): CD000019

Evidence

Obtaining the best evidence to guide clinical practice is not always easy. In particular, undertaking clinical trials to evaluate interventions for preterm infants is difficult. Although about 3000 randomised controlled trials have been reported in the field of neonatology, many interventions have not yet been subjected to unbiased evaluation. This could be because the trials have not been attempted, or have been flawed methodologically, or have been too small to detect clinically important effects. Large perinatal trials have problems with recruitment. This could be related to the issues surrounding the public perception of perinatal trials and the need for (and difficulty in obtaining) informed consent from parents. Even when perinatal trials have been undertaken successfully, in some studies follow up has been too short and has assessed short term or surrogate outcomes for preterm infants.

Levels of evidence for effects of treatments—limiting bias

- Systematic review of all relevant randomised controlled trials
- Large multicentre randomised controlled trials
- Controlled trials without randomisation
- Cohort studies
- Case controlled studies
- Multiple time series
- Before and after studies
- Opinions based on clinical experience or expert committee

Difficulties in undertaking randomised controlled trials

- Limited infrastructure to support studies
- Large trials needed to detect modest effect sizes—trials need to be multicentre or multinational, or both
- Limited funding—perinatal health not viewed as a funding priority
- Limited potential for industrial partnership
- Trial recruitment undertaken by busy clinicians or carers
- Validity of informed consent obtained at stressful times
- Public perception of perinatal research
- Need for long term follow up

The need for large trials

The introduction of antenatal steroids and exogenous surfactants is associated with about a 40% reduction in the risk of mortality. Future interventions for preterm infants will probably not have the same major beneficial effects as each of these interventions.

Evidence based care should be informed by the best quality evidence for the effect of interventions on clinically important longer term outcomes

Future trials must be designed to detect much more modest (but clinically important) effects. These trials will have to recruit many mothers and infants, and be multicentre, and often multinational. Despite problems with infrastructure, support, and public perception, recent randomised controlled trials have provided answers to important questions for preterm infants, their families, and carers.

In some places—for example, in North America and Australasia—perinatal networks for undertaking multicentre trials are well established. In the United Kingdom and other countries, an administrative infrastructure for protocol development, data management, and follow up in perinatal trials needs do be formalised. Collaborative networks of perinatal units undertaking large trials will allow parent groups and researchers to prioritise their most important questions. These collaborations also ensure that competing trials do not occur simultaneously. If perinatal care is to continue to improve outcomes, all potential new interventions for preterm infants must be assessed in the most efficient way.

Which outcomes should we measure?

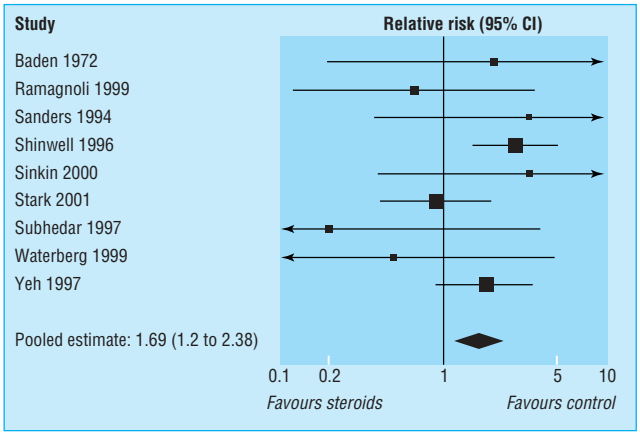
Trials must evaluate outcomes that are important to infants and their families as well as to carers and health services. To date, the major question for many interventions has been: "Does this treatment improve the chances of survival?" As advances in care of preterm infants have reduced mortality, however, the effect of interventions on morbidity in surviving infants must be considered. This is particularly important in perinatal practice as there is a potential for interventions to improve short term outcomes but also to increase the likelihood of adverse longer term outcomes in surviving infants. For example, giving preterm infants systemic corticosteroids in the first few days of postnatal life improves short term respiratory outcomes, such as allowing earlier weaning from the ventilator or reducing oxygen dependency. Trials that undertook longer term follow up, however, showed that infants who received corticosteroids had a higher rate of adverse neurological effects, including cerebral palsy.

The importance of assessing outcomes that are relevant to infants and families rather than surrogate outcomes is further illustrated by the trials of tocolytic drugs used to suppress uterine contractions and delay preterm delivery. Trials assessing these treatments have usually measured gestation at delivery as a primary outcome. Meta-analysis of these trials showed an unequivocal effect of tocolytic drugs delaying delivery. Although there is a strong relation between length of gestation and the risk of neonatal mortality and morbidity, it does not necessarily follow that delaying delivery improves important outcomes for infants. In fact, meta-analyses of trials of tocolysis have not showed any effect on perinatal mortality or morbidity, but they have shown a higher risk of maternal adverse effects. Further large randomised controlled trials with long term follow up are needed to assess if tocolysis is a benign intervention for mothers and preterm infants.

Evaluating the longer term neurodevelopmental outcomes of perinatal treatments is difficult and expensive. Abnormal motor function or severe neurosensory disability can be assessed in the second year after birth, but milder sensory problems, or behavioural problems, are more reliably assessed in older preschool children. Educational and cognitive deficits are not apparent until children are of school age. Follow up of trial cohorts must be as complete as possible as children who are difficult to follow up have a higher risk of impairment than those who are easily found.

Recent examples of large perinatal trials

Trial	Main question	Participants
CRYO-ROP (follow up)	Do the benefits of cryotherapy for threshold retinopathy of prematurity persist into later childhood?	247 children evaluated at aged 10 years (97% follow up)
TIPPS	Does indomethacin prophylaxis affect long term neurological outcomes for extremely low birthweight infants?	1202 extremely low birthweight infants from 32 centres in five countries
ORACLE	Do maternal antibiotics improve perinatal outcomes in spontaneous preterm labour, or preterm, prelabour rupture of fetal membranes?	4826 women with preterm, prelabour rupture of fetal membranes; 6295 women in spontaneous preterm labour
BOOST	Does targeting a higher oxygen saturation range in preterm infants dependent on supplemental oxygen improve growth and development?	358 infants born at less than 30 weeks of gestation (dependent on supplemental oxygen at 32 weeks of postmenstrual age)
INIS	Does polyclonal immunoglobulin improve long term outcomes for neonates with sepsis?	Ongoing: planned to recruit 5000 infants
CAP	Does management of apnoea of prematurity without methylxanthines affect survival without neurodisability in very preterm infants?	Ongoing: aiming to enrol >1000 infants weighing 500-1250 g at birth



Effect of corticosteroids given in the first few days after birth in preterm infants on incidence of cerebral palsy in survivors. Adapted from Halliday HL et al. *Cochrane Database Syst Rev.* 2004(1): CD001146

The costs of tracking and assessing large groups of children for long periods need to be planned for in the development of trials

Informed consent

Informed consent is fundamental to giving legal and ethical protection to parents and preterm infants participating in research studies. Problems arise in gaining informed consent for interventions at or around the time of birth or during emergency treatment of an infant with a life threatening condition. In such circumstances it may be difficult to have a discussion in which the parents have time to consider their options and provide fully informed consent.

Qualitative research has indicated that parents value their part in the informed consent process. However, some evidence exists that current practice in obtaining valid consent for participation in perinatal trials is flawed, especially in circumstances when parents are approached at a stressful time, such as during an emergency situation. In several large perinatal trials parents have been informed antenatally about the possible need for emergency intervention around the time of birth. This approach, which allows parents to withdraw presumed consent at any stage thereafter, may help to increase recruitment rates without compromising parental understanding of the nature and purpose of the research. The elements of the consent process valued by parents and carers need to be identified.

Recruitment of pregnant women into clinical trials is complicated because an intervention to which mother and child are exposed may cause harm as well as good

Getting evidence into practice

Bridging gaps between evidence and practice is central to ensuring that beneficial interventions are used appropriately, and harmful interventions are avoided. Busy clinicians, however, may not always be aware of all evidence based practice guidelines. Randomised controlled trials have indicated that strategies such as introducing guidelines via an opinion leader, organising group discussions and training workshops, and undertaking audit and performance feedback can promote the use of the best available evidence.

Written information and talking to parents can help improve their understanding of the research process

Conclusion

Well conducted randomised controlled trials can provide the least biased assessment of interventions to improve outcomes for preterm infants. Increasingly, these trials will be large, multicentre, international, use a simple and pragmatic protocol, and incorporate good follow up and assessment of long term outcomes. To achieve good quality research, it is essential to continue to engage with parents and patients. Care of the preterm infants is a rapidly changing field and there are frequent shifts in the weight of accumulating evidence. Systematic reviews of the results of randomised trials must be updated continuously so that the evidence base from which the clinical guidelines are developed remains valid.

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The ABC of preterm birth is edited by William McGuire, senior lecturer in neonatal medicine, Tayside Institute of Child Health, Ninewells Hospital and Medical School, University of Dundee; and Peter W Fowlie, consultant paediatrician, Perth Royal Infirmary and Ninewells Hospital and Medical School, Dundee. The series will be published as a book in spring 2005.

Competing interests: For WMcG's competing interests see first article in the series.

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Further reading

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